REMARKS

Reconsideration of this application is respectfully requested. Claims 21, 25, 27, 31, 33, and 37 are pending.

Rejections Under 35 U.S.C. §103

Claims 21, 25, 27, 31, 33, and 37 have been rejected under 35 U.S.C. §103 as obvious over Patris, *Int. Clin. Psychopharm.* 11:129-136 (1996) ("Patris") in view of U.S. Patent No. 4,943,590 ("Boegesoe") and U.S. Patent No. 4,079,135 ("Maisey"). The Examiner cites Patris as disclosing administration of citalopram to treat patients with major depression and a MADRS score of 30; but admits that Patris does not disclose escitalopram. The Examiner cites Boegesoe as disclosing that the entire 5-HT uptake inhibition activity in racemic citalopram resides in escitalopram; but admits that Boegesoe does not disclose oxalate salts. The Examiner cites Maisey as teaching an antidepressant that can be routinely converted to a crystalline oxalate salt before administration (*see* col. 4, lines 30-33; col. 8, lines 48-51; and col. 9, lines 29-59); but admits that Maisey does not disclose escitalopram. From this, the Examiner concludes that it would have been obvious to use crystalline escitalopram oxalate to treat severe depression in patients with a MADRS score of at least 29.

The rejection is traversed, and reconsideration is respectfully requested.

The presently claimed invention is directed to a method of using escitalopram to treat patients suffering from severe depression and having a MADRS score of at least 29. Claims 21, 25, 27, 31, 33, and 37 are not obvious over the cited references because, *inter alia*, (i) the present invention is associated with unexpected results because escitalopram has unexpectedly superior efficacy compared to citalopram in patients suffering from severe depression and having a MADRS score of at least 29; and (ii) one of ordinary skill in the art would not have reasonably predicted that the R-enantiomer in citalopram has a *negative* effect on escitalopram, resulting in citalopram's inferior efficacy in the claim population of severely depressed patients.

First, it is well established that "[e]vidence of unexpected results can be used to rebut a prima facie case of obviousness." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir.

2007). Here, escitalopram has been shown to be surprisingly superior to citalopram in the treatment of a particular patient population – namely, depressed patients having a MADRS score of at least 29, where the patients received comparable amounts of escitalopram (i.e., either the S-enantiomer alone or in its racemic form). Evidence of these unexpected results is found in both the specification (p. 6, line 19 to p. 7, line 9) and in scientific literature that has been previously submitted in connection with this application (*see, e.g.*, Gorman, *MedWorks Media*, 40-44 (April 2002); Lepola, *Int Clin Psychopharm*, 19:149-55 (2004); Moore, *Int Clin Psychopharm*, 20(3):131-37 (2005); Lam, *Pharmacopsychiatry*, 39:180-84 (2006); Yevtushenko, *Clinical Therapeutics*, 29(11):1-14 (2007)). Copies of Gorman (2002), Lepola (2004), Moore (2005), and Lam (2006) were submitted with the Response filed September 27, 2007; and a copy of Yevtushenko (2007) was submitted with the Response filed August 7, 2008.

The specification and each of these articles provide clinical data showing that escitalopram is significantly and surprisingly more effective than citalopram when used to treat the claimed population of depressed patients. For example, the specification states that escitalopram is "substantially more than two times as potent as the racemate" (p. 2, lines 13-15), which is important because one of ordinary skill would have expected escitalopram to be no more than twice as potent. Since it was unknown prior to the present invention that the R-enantiomer of citalopram negatively impacts the efficacy of escitalopram (p. 2, lines 13-14), one of ordinary skill would have expected administration of escitalopram to achieve the same response in a patient, but requiring only half the dose to do so. But surprisingly, escitalopram was found to be much more effective than citalopram in treating the specific population of patients suffering from severe depression and having a MADRS score of at least 29.

This early understanding of the expected efficacy of escitalopram in severely depressed patients is confirmed by Lepola, for example, which states (p. 149):

> In the clinical development of escitalopram, it was assumed that the therapeutically active enantiomer would have the same efficacy as the racemate (citalopram), but at half the dose. However, recent biochemical functional and behavioural experiments indicate that escitalopram has greater efficacy and a faster onset of action than equivalent doses of citalopram in nonclinical studies (Mørk *et al.*, 2003; Sánchez *et al.*, 2003a, b).

At the time the present application was filed, one of ordinary skill in the art would not have expected escitalopram to provide superior efficacy in severely depressed patients having a MADRS score of at least 29, let alone to the statistically significant degree described in the specification and confirmed in the later clinical studies. Beyond superior efficacy, escitalopram has also been found to exhibit other significant advantages over citalopram when used to treat depressed patients with a MADRS score of at least 29, including faster onset, and higher responder and remission rates. *See, e.g.*, Lepola (2004) at p. 150, left col. (describing studies in which escitalopram separated significantly from placebo as early as week 1, whereas statistically significant separation of citalopram from placebo did not occur until week 6 or later); and Moore (2005) at p. 135, left col. (describing study in which responder and remitter rates were higher at endpoint with escitalopram than with citalopram).

Furthermore, Lam (2006) reports that the statistical significance is greater as the severity of the depression (as measured by MADRS) increases. That is, escitalopram is better than citalopram overall, and was shown to be particularly better in patients with higher MADRS scores. *See* Lam at pp. 183-84; Fig. 3 ("several randomized controlled trials and pooled analyses have shown superiority of escitalopram over citalopram, especially in patients with higher levels of symptomatology").

Second, at the time the application was filed, one of ordinary skill would have had no way of predicting that the R-enantiomer of citalopram has an inhibitory effect on escitalopram. The unpredictability of individual enantiomers is well known in the art. The beneficial effects of a drug may reside in the racemic form or in one of its individual enantiomers; and there is no way to predict where the beneficial activity resides merely by assessing the structure of the molecule. There is also no way to predict what type of activity each individual enantiomer may possess. For instance, one enantiomer may exhibit favorable activity (e.g., antidepressant effects), whereas the other may have no activity, some activity, antagonistic activity (e.g., against the active enantiomer), or a completely separate favorable or unfavorable activity unrelated to that of the active enantiomer. *See, e.g.*, "Case Histories in Drug Discovery and Design 2001," *Drug News Perspect* 15(1):60-64, Jan-Fed 2002 at p. 62, left col. ("More than 500 drugs

currently exist as racemates but perhaps only 5% are suitable. Unfortunately, the properties of the enantiomers are not predictable from the racemates.") (copy enclosed as Exhibit A).

This unpredictability was demonstrated in the case of fluoxetine (Prozac®), for example, which is an FDA approved racemic mixture of R-fluoxetine and S-fluoxetine. After determining that the R-enantiomer had a shorter and more desirable half-life, a study was conducted on the individual R-enantiomer. However, the results of this study showed that R-fluoxetine caused cardiotoxicity (a prolonged QT interval) that did not occur when administered in the racemic form. Hence, the more desirable enantiomer in Prozac® was *less* beneficial when administered in its enantiomerically pure form. *See* "Lilly pulls out of R-fluoxetine deal," *Scrip* 2586:24 (Oct. 25, 2000) (copy enclosed as Exhibit B); *see also Drug News Perspect* at p. 62, left col. ("[T]he properties of the enantiomers are not predictable from the racemates. For example, liver toxicity occurs with an enantiomer of **labetalol**, and QT prolongation occurs with **(*R*)-fluoxetine**.") (emphasis in original).

Given the foregoing, one of ordinary skill in the art would not have reasonably predicted that escitalopram would be more than twice as effective as citalopram in treating depressed patients having a MADRS score of at least 29, let alone that administration of escitalopram would result in both significantly faster onset of treatment and higher remission rates. Accordingly, claims 21, 25, 27, 31, 33, and 37 are not obvious over the cited references; and Applicant respectfully requests that this rejection be withdrawn.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: March 3, 2009

Respectfully submitted,

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